بسم الله الرحمن الرحيم

VITAMIN D AND CHRONIC KIDNEY DISEASE.

WHAT WE KNOW AND WHAT WE DO NOT KNOW

DR AHMED ELDEEP
M.D INTERNAL MEDICINE

AGENDA

- Vitamin D Physiology
- Classical and Non-classical actions of vitamin D
- Vitamin D metabolism in CKD
- Vitamin D Therapy in CKD

Vitamin D Physiology

- **2** Sources.
- **2** Hydroxylation reactions.
- **2** Forms
  - inactive form
  - active form
- **2** Faces (hormone/ Vitamin).
  - Not classic hormone
  - Not true “vitamin”.
- **2** Actions
  - Classical
  - Non classical

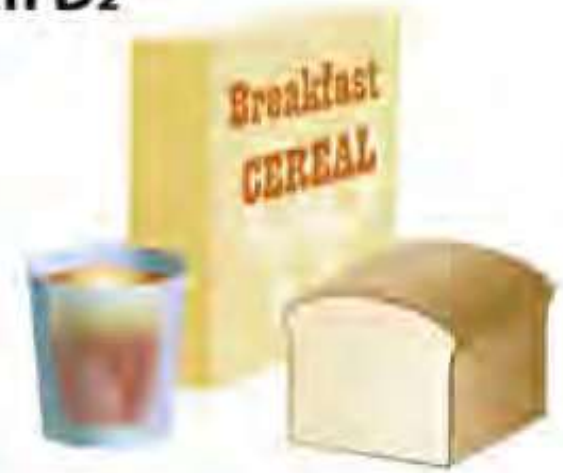
2 Sources.

- Foods
  - Naturally found in very few foods
  - Added to many foods on the market
- Sunlight

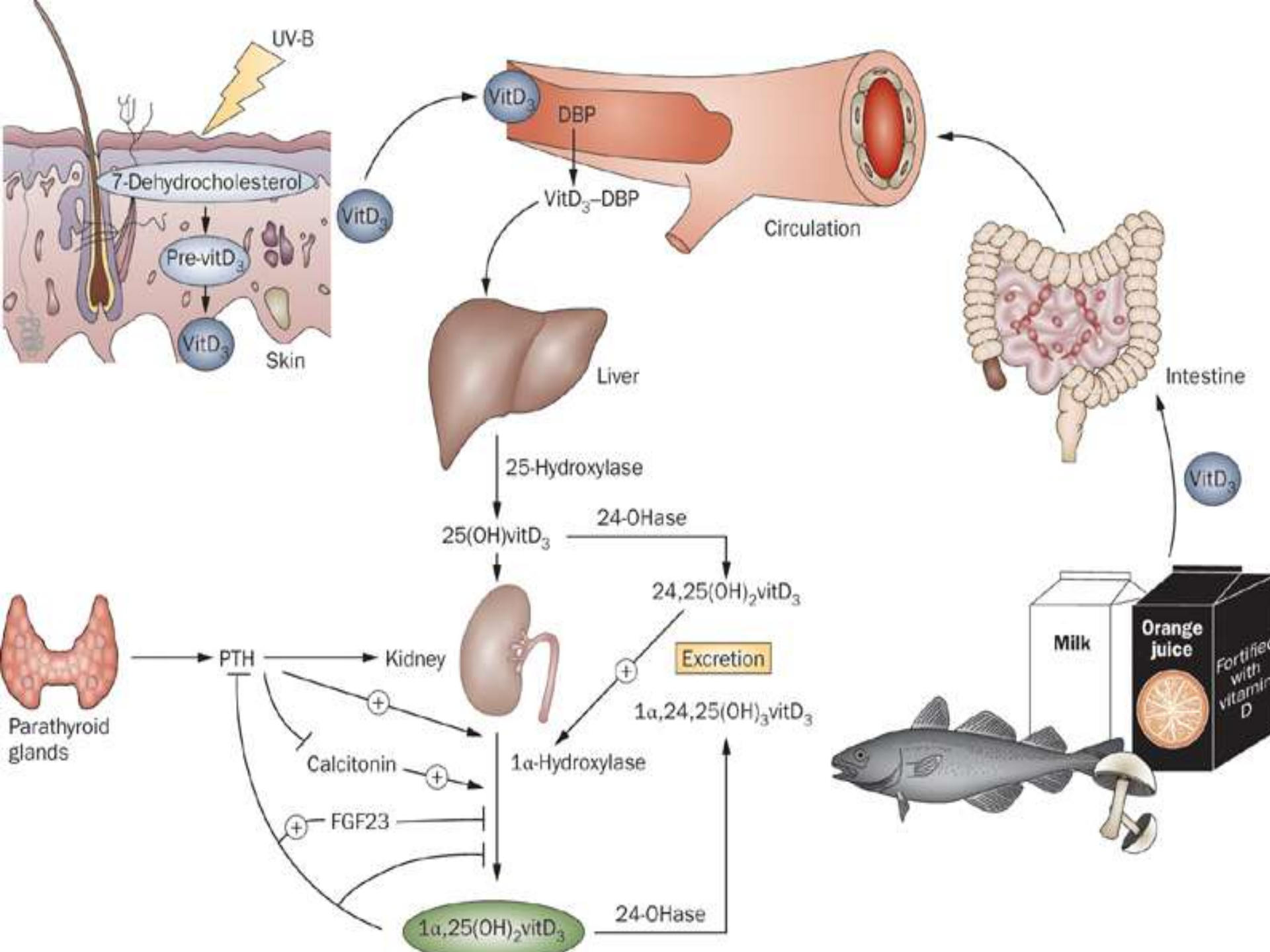
Vitamin D_3

Synthesized in skin and occurs naturally in oily fish and is added to milk.
Vitamin D_3 (cholecalciferol).

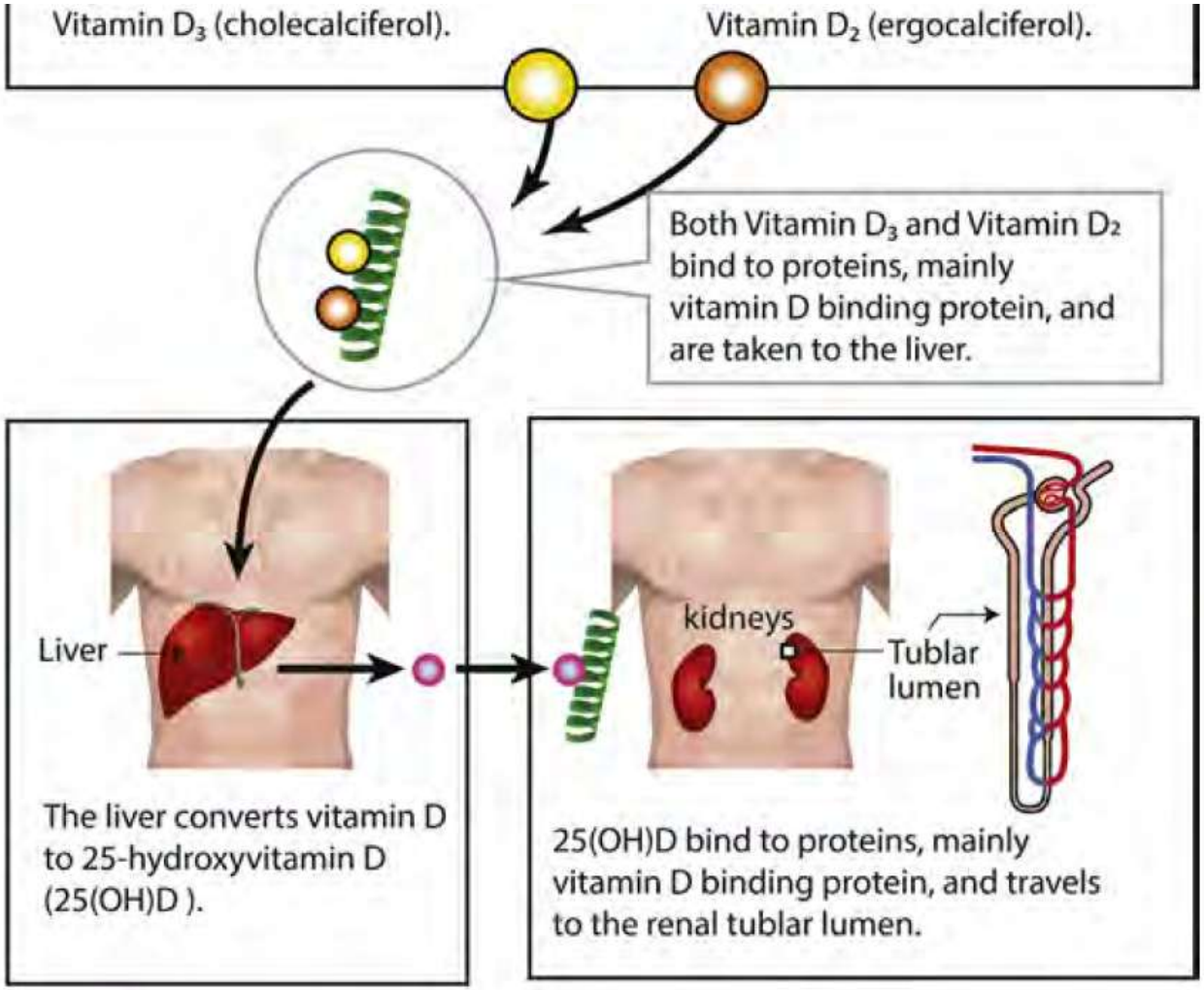
Vitamin D_2

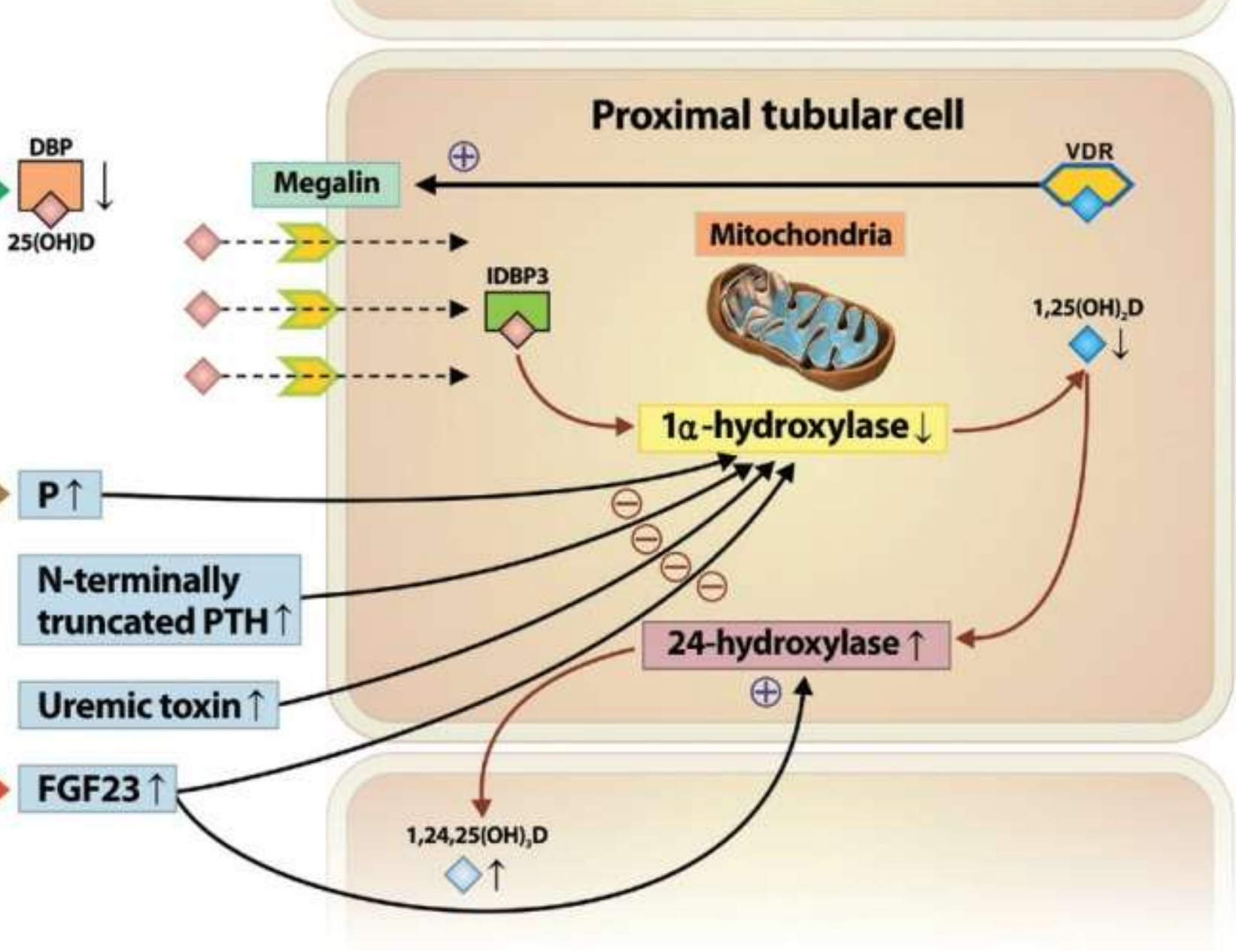


Produced through UV irradiation of yeast ergosterol and added to many foods.
Vitamin D_2 (ergocalciferol).


UV-B
7-Dehydrocholesterol
Pre-vitD3
VitD3
Skin
VitD3
VitD3
DBP
VitD3–DBP
Circulation
Liver
25-Hydroxylase
25(OH)vitD3
24-OHase
24,25(OH)2vitD3
Excretion
Intestine
VitD3
Milk
Orange juice
Fortified with vitamin D
Parathyroid glands
PTH
Kidney
Calcitonin
FGF23
1α-Hydroxylase
1α,24,25(OH)3vitD3
1α,25(OH)2vitD3
24-OHase

2 hydroxylation reactions




Proximal tubular cell
DBP
25(OH)D
Megalin
VDR
Mitochondria
IDBP3
1,25(OH)2D
1α-hydroxylase ↓
P ↑
N-terminally truncated PTH ↑
24-hydroxylase ↑
Uremic toxin ↑
FGF23 ↑
1,24,25(OH)3D ↑

2 Forms

The difference in characteristics of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D.

	Affinity to vitamin D receptor	Serum total concentration	Half-life	Risk of hypercalcemia
25(OH)D	(1)*	9.0–34.0 ng/mL (500)*	480 hrs	Low
$1,25(OH)_2D$	(100–200)*	20–60 pg/mL (1)*	15 hrs	High

* Relative value

25(OH)D

Longer halflife

major biomarker of total vitamin D stores

Has a binding capacity, albeit weak, for vitamin D receptors (VDR),

considered as an indicator of vitamin D sufficiency.

Has hundred times higher blood concentration than 1,25(OH)2D

1,25(OH)2D

- The biologically active
- Not reflect overall vitamin D status ……
- Very short half-life (hours) because of its lower affinity for DBP.
- Formation is not directly regulated by vitamin D intake or cutaneous synthesis.
- Regulated tightly (1α-hydroxylase) by

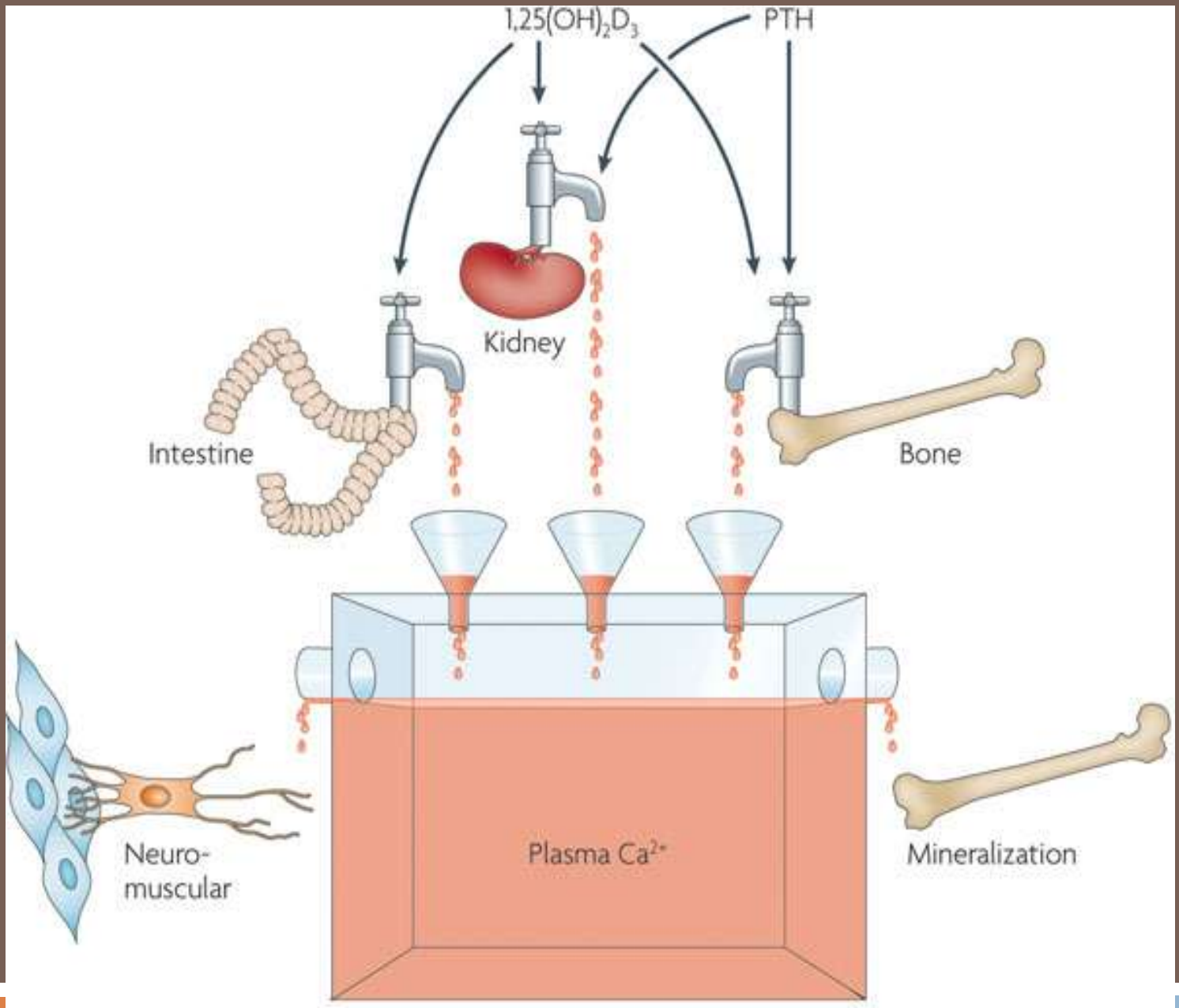
Hindawi Publishing Corporation Disease Markers Volume 2015, Article ID 868961

2 Faces (hormone/ Vitamin).

- Not a classic hormone because it is not produce and secreted by an endocrine "gland."
- Not a true "vitamin" since it can be synthesized *de novo*.
- Vitamin D is a true hormone that acts on distant target cells to evoke responses after binding to high affinity receptors

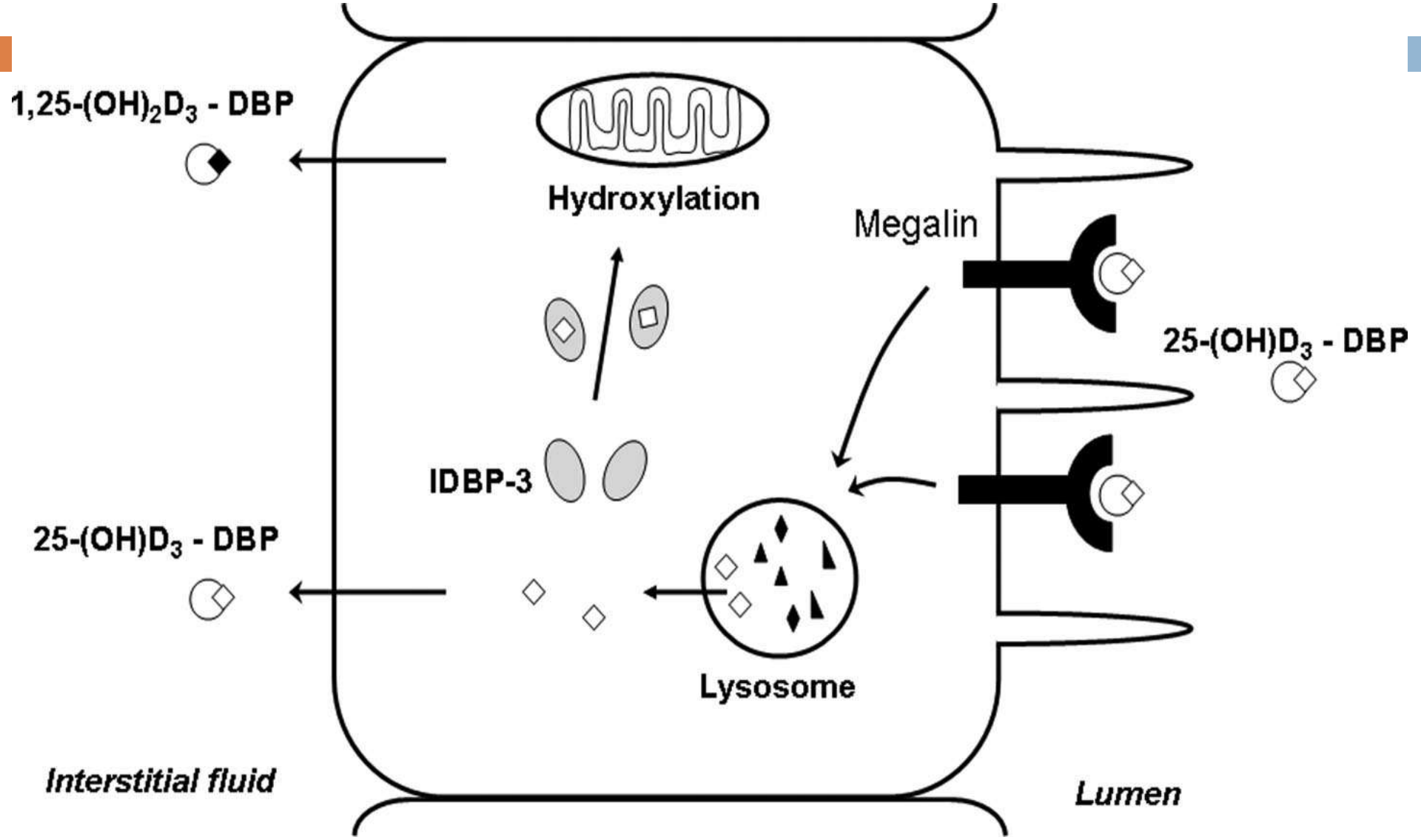
2 Actions

Classical actions



Nature Reviews | Drug Discovery

Roles of megalin and intracellular vitamin D binding protein 3 (IDBP-3) in the delivery and 1-hydroxylation of 25-hydroxyvitaminD.



AJP-Renal Physiol • VOL 289 • JULY 2005 • www.ajprenal.org

Non-classical actions

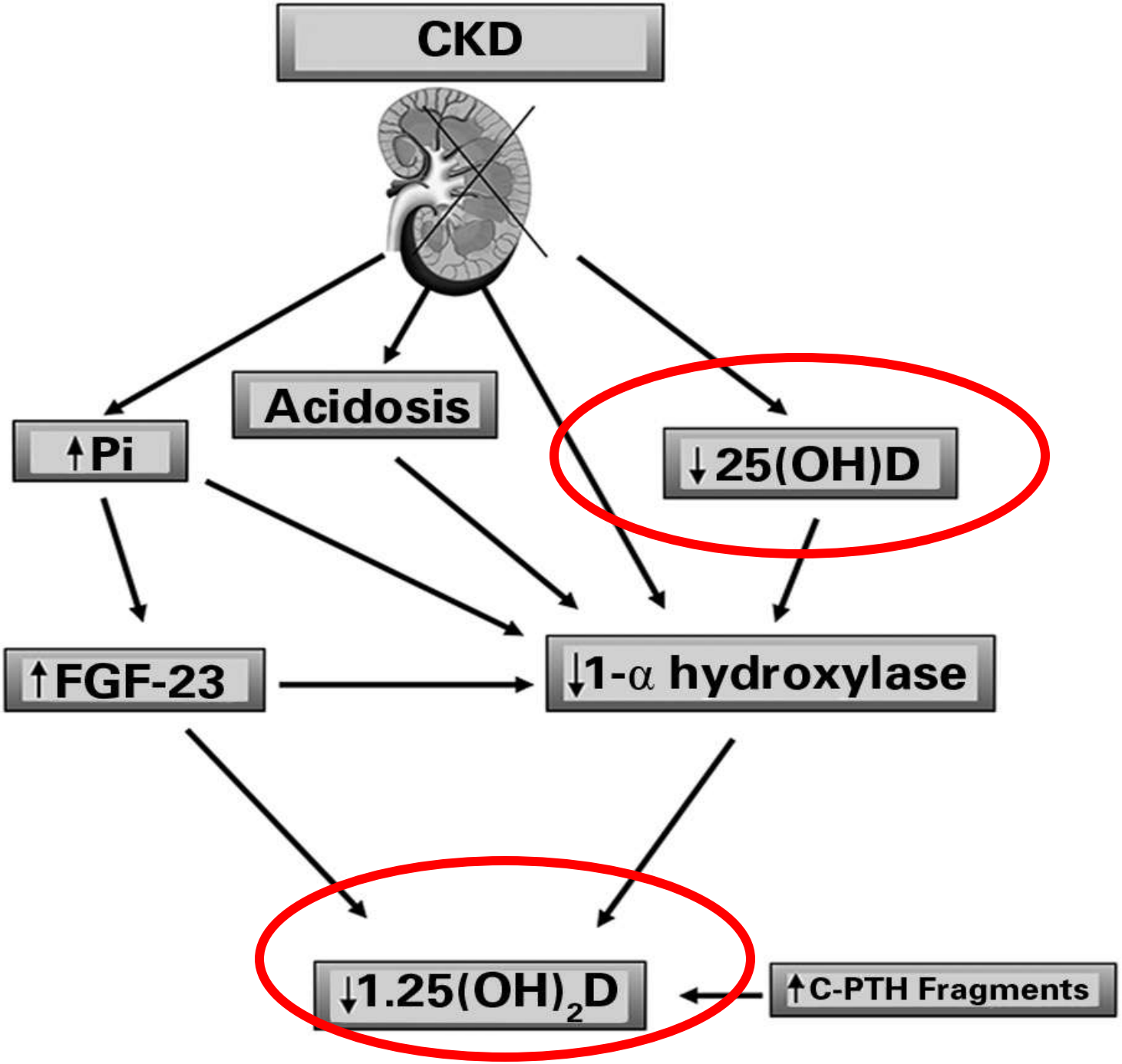
- Calcium-phosphorus-PTH axis domain.

- 1-α-hydroxylase in tissues and organs other than kidneys.

- Modulation of the immune system,
- Regulation of cellular differentiation,
- Programmed cell death,
- Inhibition of cell growth,
- Control of the central nervous system,
- Regulation of cardiomyocyte hypertrophy,
- Regulation of insulin secretion and
- Regulation of blood pressure via (RAAS).

J Bras Nefrol 2013;35(4):323-331

Vitamin D metabolism in CKD


CKD
↑Pi
Acidosis
↓25(OH)D
↑FGF-23
↓1-α hydroxylase
↓1.25(OH)2D
↑C-PTH Fragments

Calcidiol deficiency

Calcitriol deficiency

Calcitriol resistance

Nigwekar SU, Bhan I, Thadhani R. Ergocalciferol and cholecalciferol in CKD. Am J Kidney Dis 156–60:139;2012

Calcidiol deficiency

Calcitriol deficiency

Calcitriol resistance

adhani R. Ergocalciferol and cholecalciferol in CKD. Am J Kidney Dis
156–60.139;2012

Calcidiol deficiency

- Reduced sun exposure,
- reduced skin synthesis,
- reduced ingestion of foods rich in vit. D,
- loss of DBP with proteinuria

Calcitriol deficiency

Calcitriol resistance

Nigwekar SU, Bhan I, Thadhani R. Ergocalciferol and cholecalciferol in CKD. Am J Kidney Dis 156–60:139;2012

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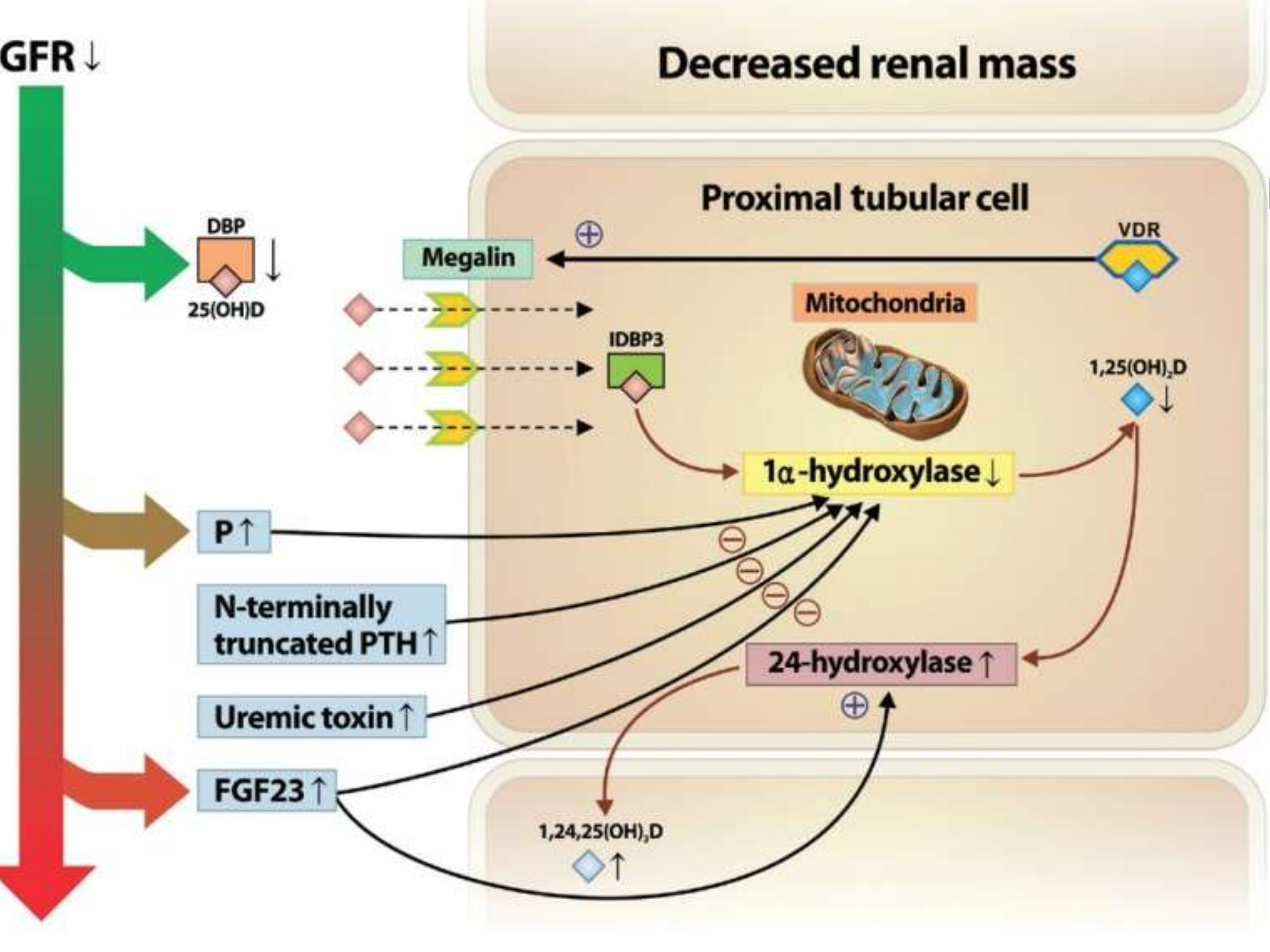

GFR ↓
Decreased renal mass
Proximal tubular cell
DBP
25(OH)D
Megalin
VDR
Mitochondria
IDBP3
1,25(OH)2D
1α-hydroxylase ↓
P ↑
N-terminally truncated PTH ↑
Uremic toxin ↑
FGF23 ↑
24-hydroxylase ↑
1,24,25(OH)3D ↑

Calcidiol deficiency

Calcitriol deficiency

- Reduced **calcidiol** availability,
- Reduced **renal 1-ahydroxylase** availability,
- Down regulation of renal 1-a hydroxylase from **hyperphosphatemia and FGF-23**,
- Reduced endocytotic uptake by **megalin**,
- Increased degradation of calcitriol by **PTH** and FGF-23

Calcitriol resistance

Nigwekar SU, Bhan I, Thadhani R. Ergocalciferol and cholecalciferol in CKD. Am J Kidney Dis 156–60:139;2012

Calcidiol deficiency

Calcitriol deficiency

Calcitriol resistance

- **Loss of VDR in parathyroid glands,**
- **Impaired binding of active vitamin D to VDR and**
- **Impaired binding of vitamin D–VDR complex to the VDR element**

Nigwekar SU, Bhan I, Thadhani R. Ergocalciferol and cholecalciferol in CKD. Am J Kidney Dis 156–60:139;2012

FGF-23 and vitamin D

FGF-23

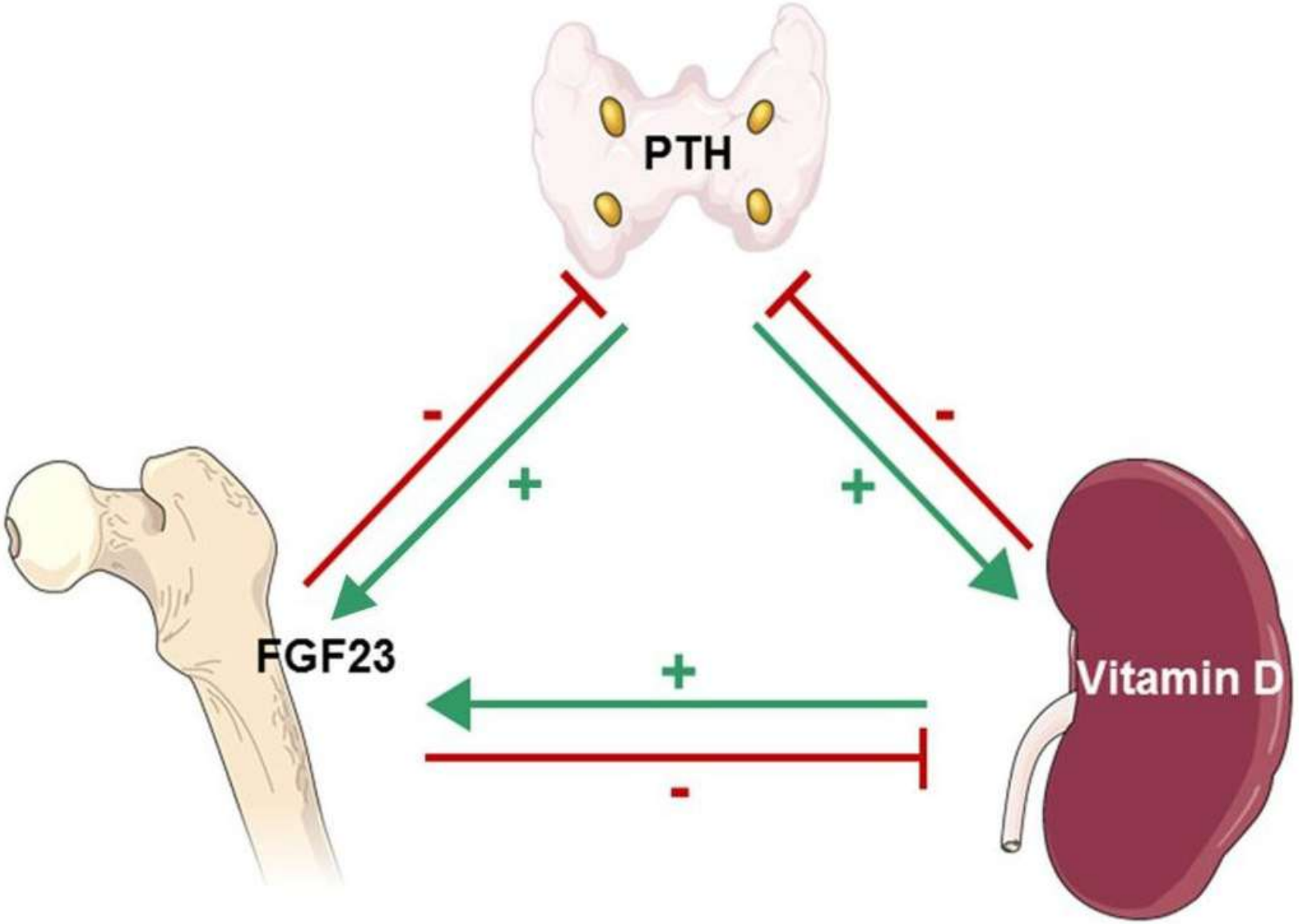
- Induces phosphaturia
- Directly suppress the activity and expression of 1-α-hydroxylase.
- Induces the expression of 24-hydroxylase the enzyme responsible for the degradation of 1.25(OH)D2 thus decreasing vitamin D bioavailability

FGF-23

Phosphaturic hormone produced by osteocytes in response to elevated phosphate.

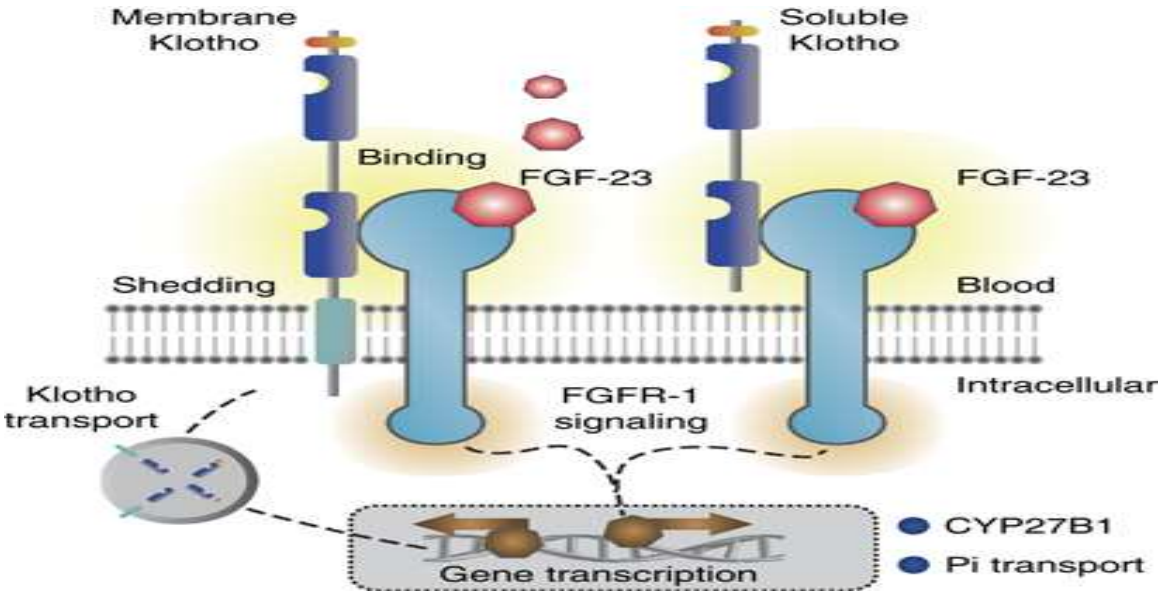
suppressing the activity of 1-α hydroxylase

Medscape


PTH
-
+
-
+
FGF23
+
-
Vitamin D

The FGF23–Klotho axis

- Klotho is a membrane-bound protein that control sodium–phosphate cotransporters and renal phosphate transport in proximal tubular epithelial cells.
- The availability of an adequate amount of Klotho is essential for FGF23 to exert its phosphaturic effects.



The FGF23-Klotho axis: endocrine regulation of phosphate. Nat Rev Endocrinol. 2009 :611-619.

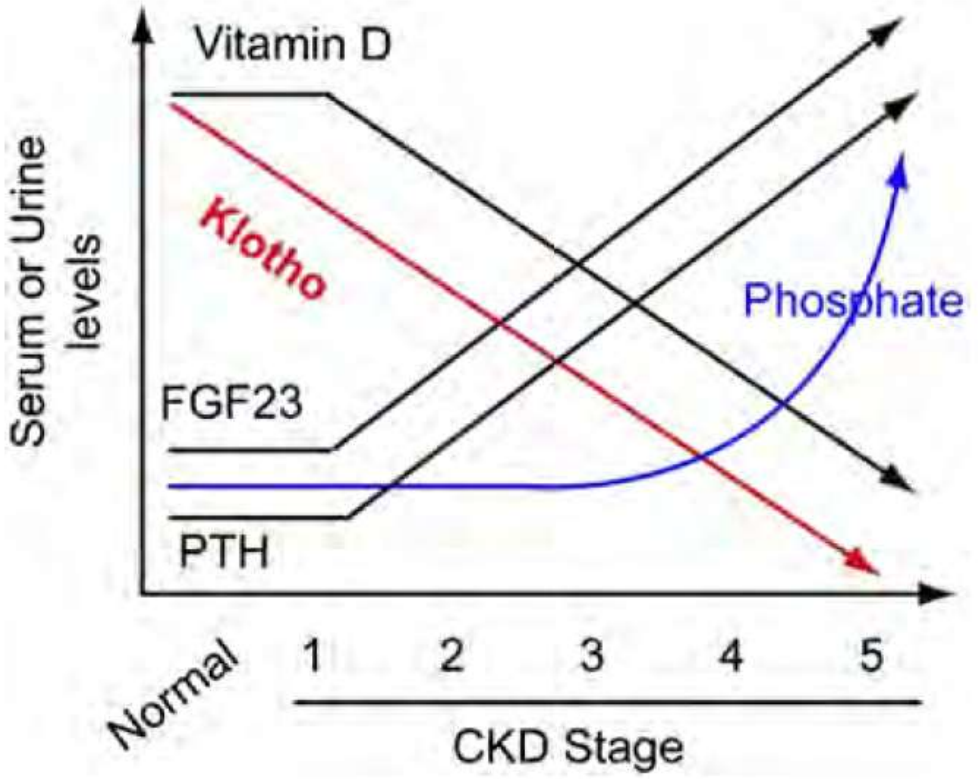


Figure 2. Changes in phosphate-regulating factors by chronic kidney disease (CKD) stages. Abbreviations: FGF23, fibroblast growth factor 23; PTH, parathyroid hormone. Reproduced from John et al[100] with permission of the National Kidney Foundation.

Am J Kidney Dis. 2014;64(4):499-509

EXTRA nephron Journals

Nephron Extra 2013;3:106–112
DOI: 10.1159/000356118
Published online: November 6, 2013

Original Paper

The Association between Fibroblast Growth Factor-23 and Vascular Calcification Is Mitigated by Inflammation Markers

Mohamed M. NasrAllah[a] Amal R. El-Shehaby[b] Noha A. Osman[a]
Tarek Fayad[a] Amr Nassef[c] Mona M. Salem[d] Usama A.A. Sharaf El Din[a]

Departments of [a]Nephrology, [b]Medical Biochemistry, [c]Radiology, and [d]Endocrinology, Kasr Al-Ainy School of Medicine, Cairo University, Cairo, Egypt

- 65 S 5 CKD on HD

Conclusion: FGF-23 is strongly correlated to various markers of inflammation and oxidative stress in hemodialysis patients. The association between FGF-23 and vascular calcification was mitigated when corrected for inflammation markers.

Kidney International, vol. 82, no. 7, pp. 737–747,.2012

The Renal Risk in Derby (RRID) study in the United Kingdom

The impact of vitamin D status on the relative increase in fibroblast growth factor 23 and parathyroid hormone in chronic kidney disease.

Taal MW, Thurston V, McIntyre NJ, Fluck RJ, McIntyre CW

Reported that intact FGF23 increased prior to PTH in patients with vitamin D sufficiency (≥20 ng/mL of serum total 25[OH]D),

1664 patients with CKD stage 3

Kidney Int. 2014 Aug;86(2):407-13.

Association between the Vitamin D Status and Clinical Outcomes in CKD

Vitamin D deficiency is highly prevalent among patients with CKD and strongly associated with various clinical outcomes.

- Doubling of serum creatinineor ESRD,
- Anemia and muscle weakness
- Vascular calcification,
- Vascular endothelial function,
- Cardiovascular events, and
- Cardiovascular mortality

Over the last 25 years, there have been many studies showingthe association between decreased calcidiol concentration in the blood and

Mortality ,

Cardiovascular disease,

Bone fractures,

Diabetes mellitus,

Some malignant diseases and autoimmune disease.

Vitamin D in CKD and Mortality

Nephrol Dial Transplant (2011) 26: 3603–3609
doi: 10.1093/ndt/gfr076
Advance Access publication 4 March 2011

Vitamin D status and mortality in chronic kidney disease

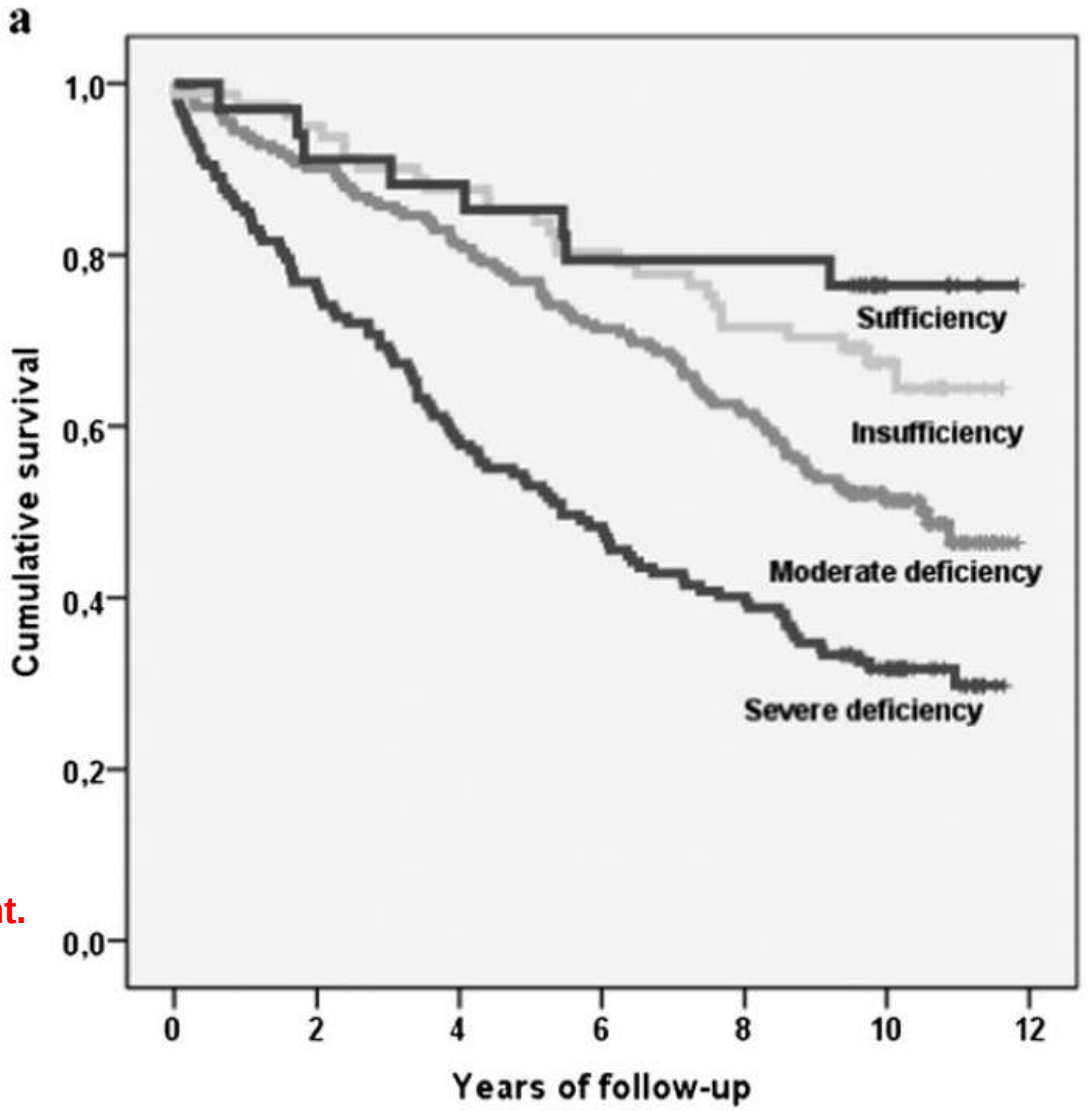
Stefan Pilz[1,2], Andreas Tomaschitz[1], Claudia Friedl[3], Karin Amrein[1], Christiane Drechsler[4], Eberhard Ritz[5], Bernhard O. Boehm[6], Tanja B. Grammer[7,8,9] and Winfried März[7,8,9]

Methods. 444 patients with eGFR <60 mL/ min/1.73m$_2$
prospective cohort study

Results. During a median follow-up time of 9.4 years, 227 patients died including 159 deaths from cardiovascular causes.

Conclusions. Low 25(OH)D levels are associated with increased all-cause and cardiovascular mortality in CKD patients.
These findings support suggestions to correct vitamin D deficiency, but whether vitamin D supplementation improves survival remains to be proven in randomized controlled trials.

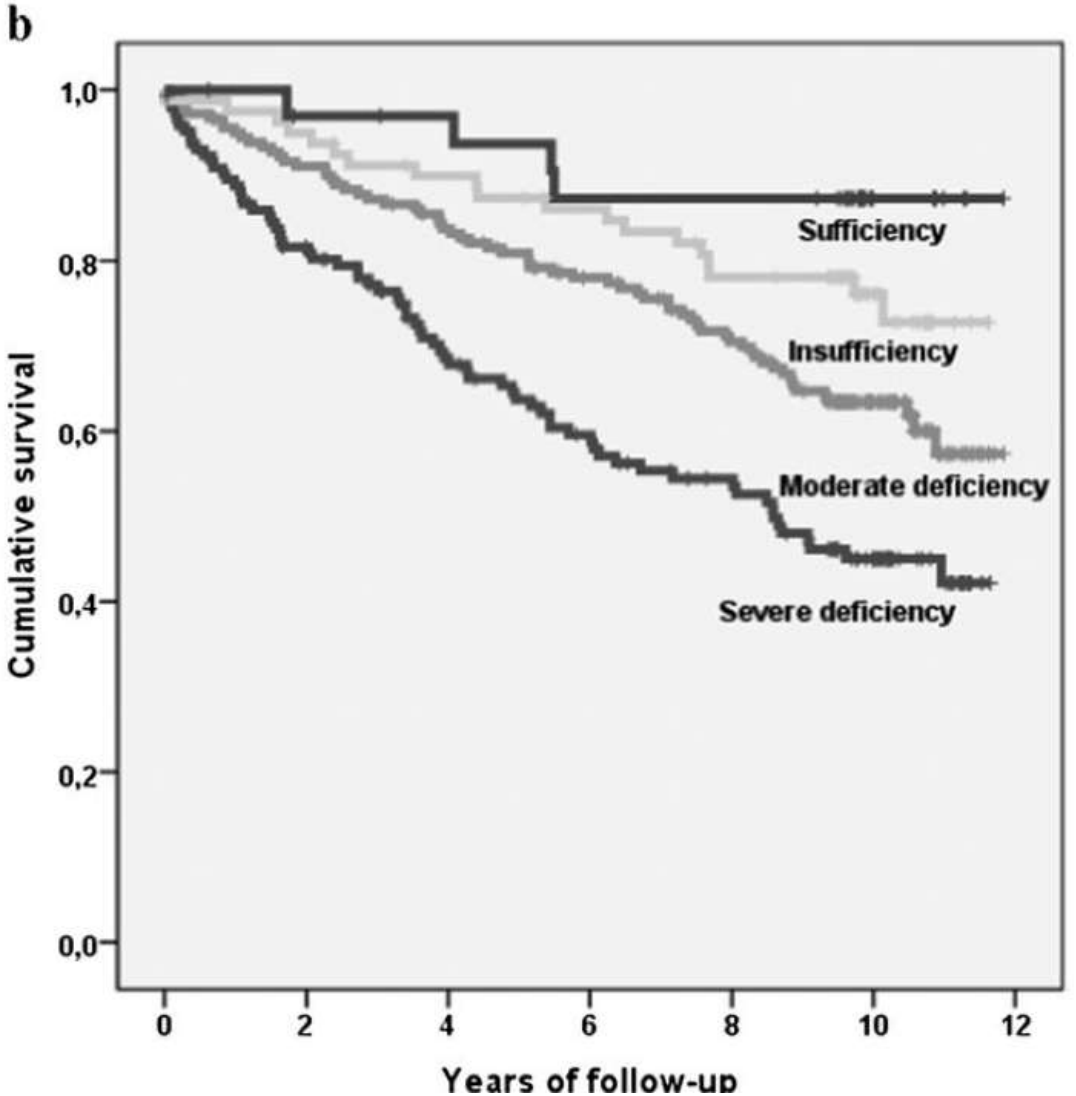
(a) Kaplan–Meier curves for all-cause mortality according to vitamin D status.



NDT
Nephrology Dialysis Transplantation

Stefan Pilz et al. Nephrol. Dial. Transplant. 2011;26:3603-3609

(b)Kaplan–Meier curves for cardiovascular mortality according to vitamin D status.



NDT
Nephrology Dialysis Transplantation

Stefan Pilz et al. Nephrol. Dial. Transplant
2011;26:3603-3609

A meta-analysis of many observational studies

Vitamin D Status and Mortality Risk in CKD: A Meta-analysis of Prospective Studies

Stefan Pilz, MD, Simona Iodice, MD, Armin Zittermann, PhD, William B. Grant, PhD, and Sara Gandini, PhD

Conclusions:

- inverse association between all-cause mortality and serum total 25(OH)D concentrations
- Higher 25(OH)D levels are associated with significantly improved survival in patients with CKD.

American Journal of Kidney Diseases, vol. 58, no. 3, pp. 374–382, 2011.

Insufficiency and deficiency

Therefore, it was obvious that vitamin D status, as a deficiency or insufficiency, should be defined.

- The definition of insufficiency and deficiency varies among researchers and organizations.
- The Institute of Medicine proposed 20 ng/mL or more of serum total 25(OH)Das an indicator of sufficiency.

- While many other views support the conventional concentration of 30 ng/mL as stated in the 2003 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines

Lab Reference Range

- INTERPRETIVE guidelines for Vitamin D (25-hydroxy):

> 80 ng/mL: Potential toxicity

30-80 ng/mL: Optimum level

20-29 ng/mL: Insufficiency

< 20 ng/mL: Deficiency

THERAPEUTIC USE OF VITAMIN D IN CKD

- The use of vitamin D compounds in CKD has been known for more than 60 years.

- Discovery of hyperparathyroidism in 1970,
- In 1976, Eastwood et al showed low levels of 25(OH)D in patients with both CKD and osteomalacia and that supplementing these patients with 25(OH)D lowers PTH levels.
- In 1975,Chertow et al discovered that administration of the active form of vitamin D, 1,25(OH)2D, reduces PTH secretion in rats

Eastwood JB, Stamp TC, Harris E, de Wardener HE. Vitamin-D deficiency in the osteomalacia of chronic renal failure. Lancet. 1976;2(7997):1209-1211

Chertow BS, Baylink DJ, Wergedal JE, Su MH, Norman AW. Decrease in serum immunoreactive parathyroid hormone in rats and in parathyroid hormone secretion in vitro b 1,25-dihydroxycholecalciferol. J Clin Invest. 1975;56(3):668-678.

Target cells for 1,25-dihydroxyvitamin D3 in intestinal tract, stomach, kidney, skin, pituitary, and parathyroid

WE Stumpf, M Sar, FA Reid, Y Tanaka, HF DeLuca

Science 07 Dec **1979**: Vol. 206, Issue 4423, pp. 1188-1190
DOI: 10.1126/science.505004

Later, however, it was discovered that the VDR is found in the parathyroid glands

Regulation by Vitamin D Metabolites of Parathyroid Hormone Gene Transcription In Vivo in the Rat

Justin Silver,* Tally Naveh-Many,* Hubert Mayer,‡ Hans Jurgen Schmelzer,‡ and Mordecai M. Popovtzer*
**Nephrology Services, Hadassah University Hospital, Jerusalem, Israel il-91120; and ‡Department of Genetics, Gesellschaft für Biotechnologische Forschung, D-3300 Braunschweig, Federal Republic of Germany*

- A major function of vitamin D is to suppress parathyroid cell proliferation and the expression of the preproparathyroid gene

These results show that 1,25(OH)2D3 regulates PTH gene transcription.

J. Clin. Invest. 78, 1296–1301 (1986).

REVIEW

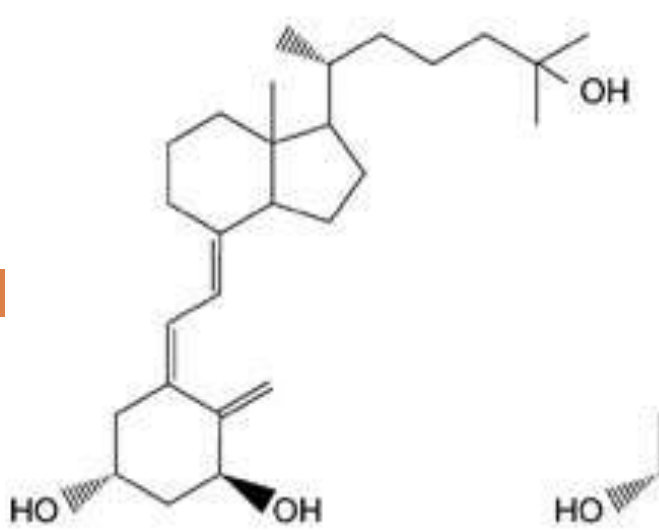
www.nature.com/clinicalpractice/endmet

Drug Insight: vitamin D analogs in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease

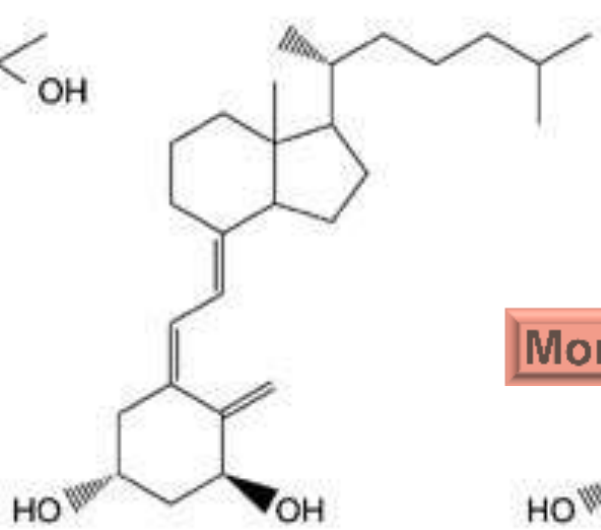
Alex J Brown* and Eduardo Slatopolsky

Nat Clin Pract Endocrinol Metab. 2007 Feb;3(2):134-44.

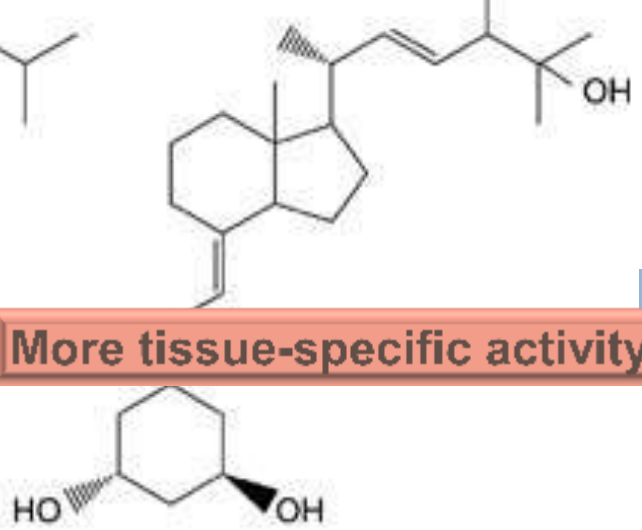
- Vitamin D analogs that inhibit PTH gene transcription and parathyroid hyperplasia (and have reduced calcemic activity)
- Safer treatment for secondary hyperparathyroidism than calcitriol;
- Greater selectivity.



$1\alpha,25(OH)_2D_3$
Calcitriol

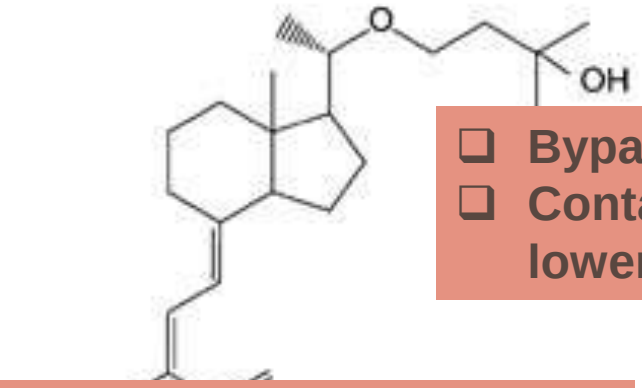


$1\alpha(OH)D_3$
Alfacalcidol

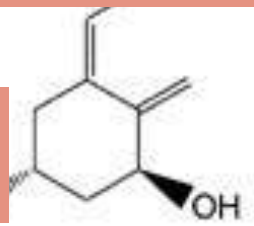


$1\alpha,25(OH)_2$-19-nor-D_2
Paricalcitol

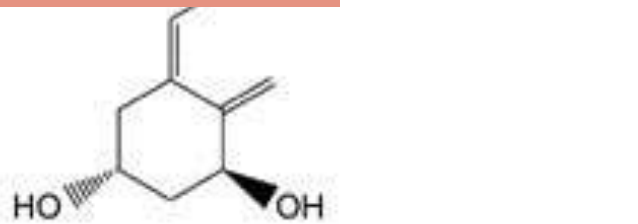
More tissue-specific activity



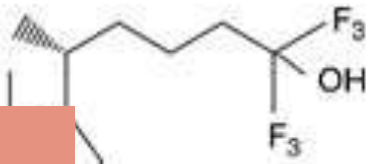
22-oxacalcitriol
Maxacalcitol



$1\alpha(OH)D_2$
Doxercalciferol



$1\alpha,25(OH)_2$-26,27-F_6-D_3
Falecalcitriol



- Bypasses first-pass metabolism
- Contains a D_2 side chain, which lowers the calcaemic liability.

- The lower toxicity (short half-life)

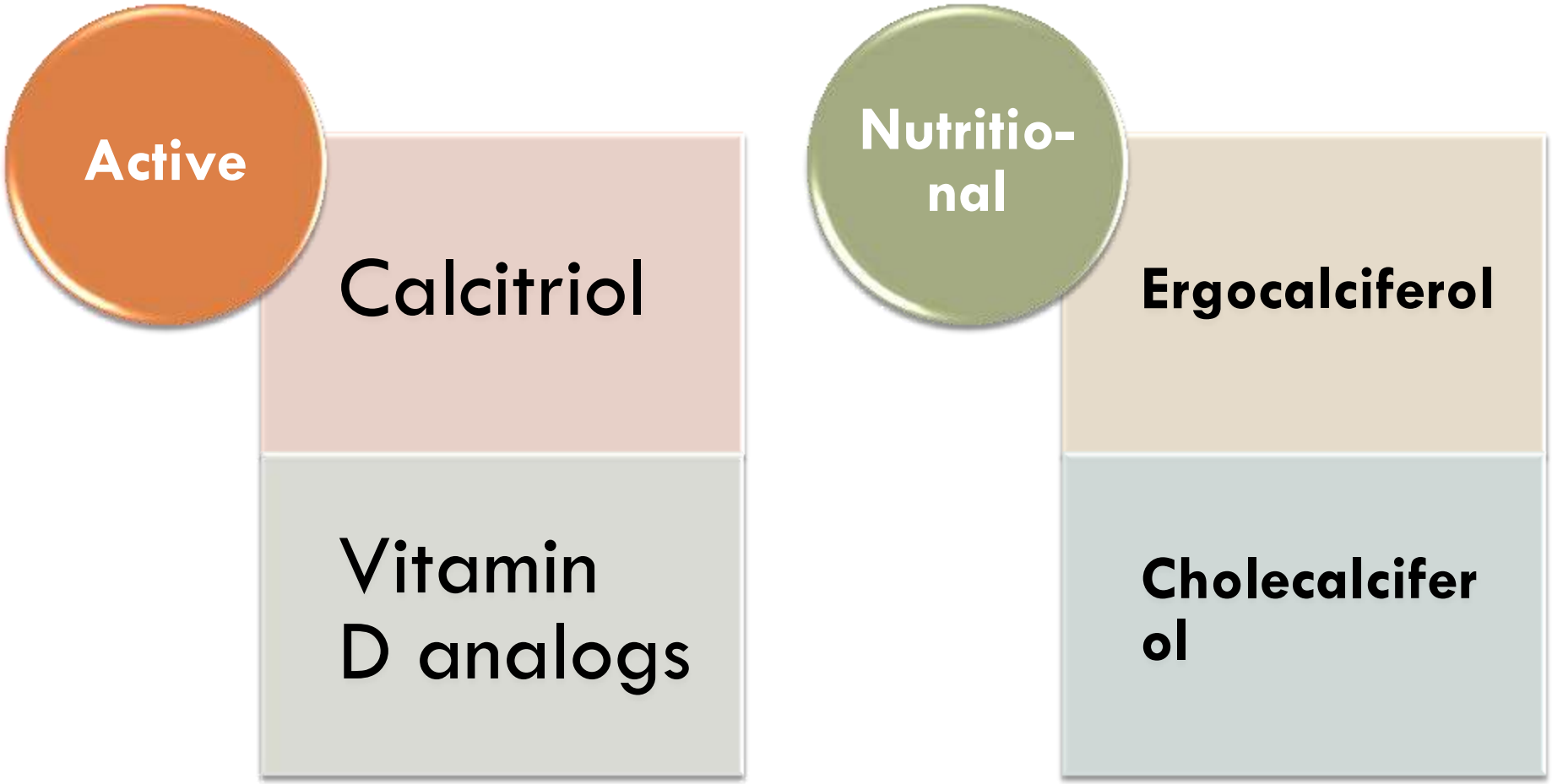
Nat Clin Pract Endocrinol Metab 3: 134–144

Vitamin D Therapy in CKD
When, to Whom and in Which Form

- The prevalence of vitamin D supplementation has rapidly increased in the United States during the past decade (from 10% in 2003 to 44% in 2011)

Journal of Renal Nutrition, vol. 24, no. 3, pp. 186–**2014 ,193**

- (Active) or (Nutritional) vitamin D in patients with CKD and ESRD.



Nutritional Vitamin D Supplementation and CKD

Nutritional vitamin D (cholecalciferol and ergocalciferol)

- **Unlikely to induce hypercalcemia** unless given continuously at a high dose because its 1α-hydroxylase-mediated activation process is regulated by many factors such as PTH, FGF23, and 24-hydroxylase .

This is **in contrast** to the effects of calcitriol and active vitamin D analogues that directly increase calcium absorption and reabsorption in the intestine and kidney tubular cells, respectively.

The American Journal of Kidney Diseases, vol. 64, no. 5, pp. 696–705, 2014.

- Concentration of <100mg/mL is generally considered safe ,
- A tolerable upper oral intake level of 4,000 IU/day .
- It forms a complex with DBP after being converted into 25(OH)D, which yields a long half-life (480 hours).
- Prescription of nutritional vitamin D at doses equivalent to weeks or months.
- Safety profile, and the low cost of nutritional vitamin D,
- No effects of nutritional vitamin D supplementation on the concentrations of FGF23

The American Journal of Clinical Nutrition, vol. 96, no. 3, pp. 672–679, 2012.

D3 OR D2

Bioavailability of Vitamin D_2 and D_3 in Healthy Volunteers, a Randomized Placebo-Controlled Trial

Ulrike Lehmann, Frank Hirche, Gabriele I. Stangl, Katja Hinz, Sabine Westphal, and Jutta Dierkes

- which form is more effective in supplementation and fortification
- 1000–1600 IU of vitamin D2 or vitaminD3 were included
- The aim was to investigate the effects of this high dose on the serum levels of the hydroxylated forms 25(OH)D2 and 25(OH)D3 and on their sum total 25(OH)D

J Clin Endocrinol Metab, November 2013, 98(11):4339–4345

Conclusions: Vitamin D3 increases the total 25(OH)D concentration more than vitamin D2.

Functionally, vitamin D3 is at least 300% more effective than D2.

Vitamin D3 supplementation has also been shown to maintain serum vitamin D levels in the long run

TREATMENT GUIDLINES

National Kidney Foundation®

K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease

American Journal of Kidney Diseases, Vol 42, No 4, Suppl 3 (October), 2003: p S3

1.4 The target range of plasma levels of intact PTH in the various stages of CKD

Table 15. Target Range of Intact Plasma PTH by Stage of CKD

CKD Stage	GFR Range (mL/min/1.73 m²)	Target "intact" PTH (pg/mL [pmol/L])
3	30-59	35-70 [3.85-7.7 pmol/L] (OPINION)
4	15-29	70-110 [7.7-12.1 pmol/L] (OPINION)
5	<15 or dialysis	150-300 [16.5-33.0 pmol/L] (EVIDENCE)

American Journal of Kidney Diseases, Vol 42, No 4, Suppl 3 (October), 2003: p S3

Table 27. Serum Levels of PTH, Calcium and Phosphate Required for Initiation of Oral Vitamin D Sterol Therapy, and Recommended Initial Doses in Patients with Stages 3 and 4 CKD

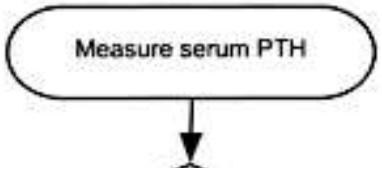
Plasma PTH pg/mL or [pmol/L]	Serum Ca mg/dL [mmol/L]	Serum P mg/dL [mmol/L]	Dose Oral Calcitriol	Dose Oral Alfacalcidol	Dose Oral Doxercalciferol
>70 [7.7] (CKD Stage 3) Or >110 [12.1] (CKD Stage 4)	<9.5 [2.37]	<4.6 [1.49]	0.25 μg/day	0.25 μg/day	2.5 μg 3x/week

8B.1 Patients treated with hemodialysis or peritoneal dialysis

Table 28. Recommended Initial Dosing for Vitamin D Sterols by Serum Levels of Intact PTH, Calcium, Phosphorus, and Ca-P Product

Plasma PTH pg/mL or [pmol/L]	Serum Ca mg/dL [mmol/L]	Serum P mg/dL [mmol/L]	Ca-P Product	Dose per HD Calcitriol†*	Dose per HD Paricalcitol*	Dose per HD Doxercalciferol†*
300-600 [33-66]	<9.5 [2.37]	<5.5 [1.78]	<55	IV: 0.5-1.5 μg Oral: 0.5-1.5 μg	2.5-5.0 μg	Oral: 5 μg IV: 2 μg
600-1000 [66-110]	<9.5 [2.37]	<5.5 [1.78]	<55	IV: 1.0-3.0 μg Oral: 1-4 μg	6.0-10 μg	Oral: 5-10 μg IV: 2-4 μg
>1000 [110]	<10.0 [2.50]	<5.5 [1.78]	<55	IV: 3.0-5.0 μg Oral: 3-7 μg	10-15 μg	Oral: 10-20 μg IV: 4-8 μg

*Intravenous; † Oral


Measure serum PTH

KDIGO 2009

- In patients with CKD stages 3-5D, the suggestions[a] are to:
  - Measure 25(OH)D (calcidiol) levels
  - Repeat testing on the basis of:
    - Baseline values
    - Therapeutic interventions
  - Correct vitamin D deficiency and insufficiency in accordance to treatment strategies recommended for the **general population**

a. 3.1.3 (2C)

KDIGO. Kidney Int. 2009; 76 (Suppl 113):S1-S130

KDIGO 2012

Vitamin D supplementation and bisphosphonates in people with CKD

3.3.5: We suggest not to routinely prescribe vitamin D supplements or vitamin D analogs, in the absence of suspected or documented deficiency, to suppress elevated PTH concentrations in people with CKD not on dialysis. (2B)

Kidney International Supplements (2013)

2013 KDIGO Controversies Conference

for updating clinical practice guidelines.

Moderate PTH elevations may serve as a beneficial adaptive response (e.g., phosphaturia, bone turnover , calcium balance and load)

Table 4 | Recommendations related to vitamin D and PTH requiring literature reassessment

4.2.1	In patients with CKD stages 3–5 not on dialysis, the optimal PTH level is not known. However, we suggest that patients with levels of intact PTH above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency (2C). It is reasonable to correct these abnormalities with any or all of the following: reducing dietary phosphate intake and administering phosphate binders, calcium supplements, and/or native vitamin D (not graded).
4.2.2	In patients with CKD stages 3–5 not on dialysis, in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, we suggest treatment with calcitriol or vitamin D analogs (2C).

Abbreviations: CKD, chronic kidney disease; PTH, parathyroid hormone.

High values may negatively impact bone quality, result in the progression of parathyroid hyperplasia and decrease the efficacy of treatment strategies.

Kidney International advance online publication, 4 February 2015; doi:10.1038/ki.2014.425

TAKE HOME MESSAGE

- Although 1,25(OH)2D The biologically active , but 25(OH)D is the major biomarker of total vitamin D stores.
- 1-α-hydroxylase is expressed in many tissues and organs other than kidneys.
- Vitamin D deficiency is highly prevalent among patients with CKD and strongly associated with various clinical outcomes.
- Vitamin D3 is at least more effective than D2.

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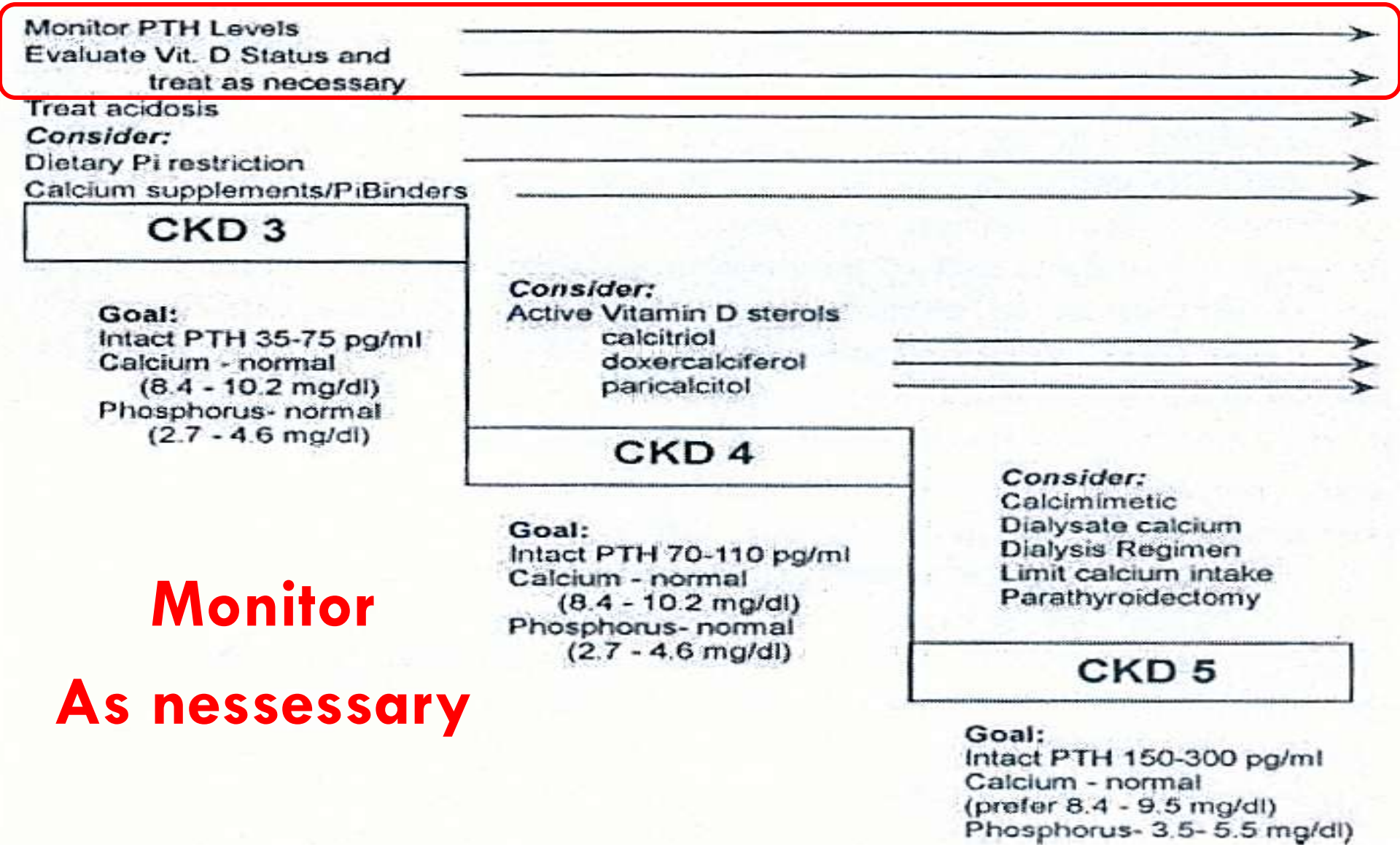
Monitor PTH Levels
Evaluate Vit. D Status and
treat as necessary
Treat acidosis
Consider:
Dietary Pi restriction
Calcium supplements/PiBinders
CKD 3
Goal:
Intact PTH 35-75 pg/ml
Calcium - normal
(8.4 - 10.2 mg/dl)
Phosphorus- normal
(2.7 - 4.6 mg/dl)
Consider:
Active Vitamin D sterols
calcitriol
doxercalciferol
paricalcitol
CKD 4
Goal:
Intact PTH 70-110 pg/ml
Calcium - normal
(8.4 - 10.2 mg/dl)
Phosphorus- normal
(2.7 - 4.6 mg/dl)
Consider:
Calcimimetic
Dialysate calcium
Dialysis Regimen
Limit calcium intake
Parathyroidectomy
CKD 5
Goal:
Intact PTH 150-300 pg/ml
Calcium - normal
(prefer 8.4 - 9.5 mg/dl)
Phosphorus- 3.5- 5.5 mg/dl)
Monitor
As nessessary

Please

Don’t overuse

Don’t abuse

Don’t misuse


Thank you